PATENT SPECIFICATION

NO DRAWINGS

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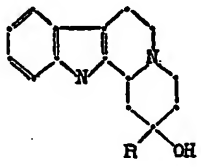
COMPLETE SPECIFICATION

Novel Quinolizine Derivatives and a process for the Manufacture thereof

We, ROCHE PRODUCTS LIMITED, a British Company, of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel quinolizine derivatives (more particularly, indolo[2,3-a]-quinolizine derivatives) and with a process for the manufacture thereof.

The novel indolo[2,3-a]quinolizine derivatives provided by the invention are substances of the general formula:



in which R stands for a phenyl, alkyl, alkenyl or alkynyl group; that is to say, they are 2 - R - 2 - hydroxyl - 1,2,3,4,6,7,12,12b-octahydro - indolo[2,3 - a]quinolizines. They have a sedative and hyptotensive activity and are intended for use in medicine.

According to the process provided by the invention, the novel substances aforesaid are manufactured by treating 2 - oxo - 1,2,3,4,6,7,12,12b - octahydro - indolo[2,3 - a]quinolizine with a GRIGNARD reagent of the formula R—Mg—Halogen or a metallo-hydrocarbon of the formula R—Metal (wherein in both formulae R has the same significance as given hitherto) under conditions which minimise the precipitation of the resulting metal complex, hydrolysing said complex and, if desired, hydrogenating the resulting 2 - R - 2-hydroxy - 1,2,3,4,6,7,12,12b - octahydro-indolo[2,3 - a]quinolizine (wherein R has the same significance as given hitherto), so as to reduce any multiple bond contained in the group R therein.

The oxo compound used as the starting material is a known compound [GROVES and SWAN, J.C.S., 1952, 650].

Preferred metallo-hydrocarbons are lithium-phenyl, -alkyls, -alkenyls and -alkynyls.

When carrying out the treatment with the GRIGNARD reagent or a metallo-hydrocarbon, it should be borne in mind that the metal compound also reacts at the indolic >NH of the oxo compound used as the starting material. Accordingly, it is necessary to use sufficient GRIGNARD reagent or metallo-hydrocarbon to cater for this. It is also necessary to carry out the treatment under conditions which prevent the precipitation of the metallo-indolyl complex. If the treatment is carried out in the most usual solvents for GRIGNARD and metal-alkyl reagents (e.g. diethyl ether) there is an immediate precipitate of insoluble complex and no reaction occurs with the ketone. It is therefore necessary to use solvent in which the said complex is soluble. Dry anisole has been found a useful solvent when using a GRIGNARD reagent and dry toluene has been found suitable when using alkyl-lithium compounds. The treatment using a lithium-acetylide can be carried out in anhydrous liquid ammonia.

A suitable method for hydrolysing the metal complex formed by the said treatment is to treat the complex with a solution of ammonium chloride in water. The hydrogenation of those hydrolysis products which contain alkenyl or alkynyl groups in position 2 may be effected using the usual hydrogenation catalysts. The alkynyl groups can be partially hydrogenated

[*Price 3s. 6d.*]

by hydrogenation in the presence of lead-inhibited palladium catalysts.

In order that the process of the invention may be more clearly understood and readily carried into effect, the following examples are now given:—

EXAMPLE 1

Methyl-magnesium iodide was prepared in dry anisole (250 ml.) from methyl iodide (23.5 g.) and magnesium (4.2 g.). A warm solution of 2 - oxo - 1,2,3,4,6,7,12,12b - octahydro-indolo[2,3 - a]quinolizine (10 g.) was added dropwise to the solution of the GRIGNARD reagent which was kept at 18°—20° C. by immersion in a cold water bath. The mixture was stirred at *ca* 20° C. for 2 hours and then treated with a solution of ammonium chloride (18 g.) in water (100 ml.). The solution was filtered and the layers separated. The aqueous phase was extracted three times, each time with 50 ml. of ethyl acetate, and the combined organic layers dried over anhydrous magnesium sulphate and evaporated under reduced pressure. The gummy residue was dissolved in hot benzene (50 ml.) and, on cooling, crystals were deposited; m.p. 200°—204° C. Purification of these crystals by chromatography on basic alumina followed by crystallisation from ethyl acetate/light petroleum (b.p. 60°—80° C.) gave colourless rhombic plates; m.p. 219°—221° C. (decomp.) of a 2 -methyl - 2 - hydroxy - 1,2,3,4,6,7,12, 12b - octahydro - indolo[2,3 - a]quinolizine racemate. The other possible racemate was isolated from the benzene mother liquors by chromatography on basic alumina. Unchanged ketone was eluted first, followed by a very little more of the last named racemate and finally the second racemate which crystallised from ethyl acetate/light petroleum (b.p. 60°—80° C.) to give colourless needles; m.p. 255°—258° C. (decomp.).

EXAMPLE 2

Phenyl-magnesium bromide was prepared in dry ether from bromo-benzene (12.56 g.) and magnesium (2.02 g.). The ether was evaporated until no more could be removed at atmospheric pressure with a bath temperature of 70° C. and then dry anisole (100 ml.) was added. The temperature of the bath was kept at 40° C. and a warm solution of 2 - oxo-1,2,3,4,6,7,12,12b - octahydro - indole[2,3-a]quinolazine added dropwise to the stirred solution. When the addition was complete, the bath temperature was maintained at 40° C. for a further 2.5 hours. The solution was cooled and treated with ammonium chloride (9 g.) in water (100 ml.). The solution was filtered and the layers separated. The aqueous phase was extracted with ethyl acetate (three times with 50 ml.) and the combined organic layers dried over anhydrous magnesium sulphate and evaporated under reduced pressure. The residue crystallised on the addition of ether (20 ml.) and was recrystallised from ethyl acetate/light petroleum (b.p. 60°—80° C.) to give colourless or pale yellow micro-crystals; m.p. 214°—216° C. (decomp.) of a 2 -phenyl - 2 - hydroxy - 1,2,3,4,6,7,12, 12b - octahydro - indolo[2,3 - a]quinolizine racemate. Chromatography of the combined mother liquors on basic alumina gave first a further quantity of this racemate and then a further racemate which crystallised from benzene/light petroleum (b.p. 60°—80° C.) to give colourless rhombohedra; m.p. 231°—232° C. (decomp.).

EXAMPLE 3

Butyl-lithium was prepared in dry ether from lithium (2.3 g.) and butyl bromide (17.3 ml.) in an atmosphere of nitrogen. The ether was evaporated and replaced by dry toluene (50 ml.). A warm solution of 2 - oxo - 1,2,3, 4,6,7,12, 12b - octahydro - indolo[2,3 - a]-quinolizine (9.6 g.) in dry toluene (400 ml.) was added dropwise to the chilled butyl-lithium solution and when the addition was complete the solution was stirred at 0° C. for 15 minutes and then allowed to come to *ca* 20° C. during 45 minutes. The solution was treated with water (100 ml.) and the layers separated. The aqueous phase was extracted with ethyl acetate (three times with 50 ml.) and the combined organic layers dried and evaporated under reduced pressure. The residue was treated with ether and ethyl acetate and the precipitated crystalline solid collected and identified as unchanged ketone. The mother liquors were purified by chromatography and gave one of the two expected racemates of 2 - butyl - 2 -hydroxy - 1,2,3,4,6,7, 12,12b - octahydro - indolo[2,3 - a]quinolizine; m.p. 207°—210° C.

EXAMPLE 4

A solution of lithium amide was prepared in anhydrous liquid ammonia (400 ml.) from lithium (1.11 g.) in the presence of a trace of ferric nitrate. Dry acetylene gas was then passed through the stirred lithium amide solution for one hour. Dry, finely powdered 2-oxo - 1,2,3,4,6,7,12,12b - octahydro - indolo-[2,3 - a]quinolizine (9.6 g.) was added, and washed in with a little dry diethyl ether and the passage of dry acetylene continued through the stirred solution. After a further 1.5 hours, the stream of acetylene was stopped and, after a further 2.5 hours, solid ammonium chloride (17 g.) was added and the ammonia allowed to evaporate. The residue was treated with water and the solid collected and washed with water. Crystallisation from ethanol gave light brown polyhedral plates which, on recrystallisation from ethyl acetate/light petroleum (b.p. 60°—80° C.) in the presence of charcoal, gave colourless polyhedral plates of 2-ethynyl 2 - hydroxy - 1,2,3,4,6,7,12,12b - octahydro - indolo[2,3 - a]quinolizine; m.p. 204°—206° C. (decomp.). On this scale only one racemate was isolated.

2 - ethynyl - 2 - hydroxy - 1,2,3,4,6,7,12,

12b - octahydro - indolo[2,3 - a]quinolizine (0.665 g.) in pure ethyl acetate (100 ml.) was hydrogenated in the presence of a lead-inhibited palladium catalyst (0.25 g.) and a small quantity of quinoline (0.25 ml. of 5% solution of quinoline in ethyl acetate). One molecular equivalent of hydrogen was rapidly absorbed. The solution was filtered, evaporated to a small volume and an equal volume of light petroleum ether was added. There precipitated 2 - vinyl - 2 - hydroxy - 1,2,3,4,6,7,12,12b - octahydro - indolo [2,3 - a]quinolizine in fine needles; m.p. = 183°—186° C. (decomp.). This substance was recrystallized from light petroleum ether (boiling range 60°—80° C.)/ethyl acetate to give colourless needles of melting point 188°—190° C. (decomp.).

WHAT WE CLAIM IS:—

1) 2 - R - 2 - hydroxy - 1,2,3,4,6,7,12,12b-octahydro - indolo[2,3 - a]quinolizines in which R stands for a phenyl, alkyl, alkenyl or alkynyl group.

2) A substance as claimed in claim 1, wherein R stands for the methyl group.

3) A substance as claimed in claim 1, wherein R stands for the phenyl group.

4) A substance as claimed in claim 1, wherein R stands for the butyl group.

5) A substance as claimed in claim 1, wherein R stands for the ethynyl group.

6) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises treating 2 - oxo - 1,2,3,4,6,7,12,12b - octahydro - indolo[2,3 - a]-quinolizine with a GRIGNARD reagent of the formula R—Mg—Halogen or a metallo-hydrocarbon of the formula R—metal (wherein in both formulae R has the significance given in claim 1) under conditions which minimise the precipitation of the resulting metal complex, hydrolysing said complex and, if desired, hydrogenating the resulting 2 - R - 2-hydroxy - 1,2,3,4,6,7,12,12b - octahydro-indolo[2,3 - a]quinolizine (wherein R has the significance given in claim 1) so as to reduce any multiple bond contained in the group R therein.

7) A process in accordance with claim 6, wherein the conditions which minimise the precipitation of the metal complex comprise the use of dry anisole as a solvent when using a GRIGNARD reaction.

8) A process as claimed in claim 6, wherein the conditions which minimise the precipitation of the metal complex comprise carrying out the treatment in dry toluene when using alkyl-lithium compounds and in anhydrous liquid ammonia when using a lithium-acetylide.

9) A process in accordance with any one of the preceding process claims wherein the hydrolysis of the metal complex is brought about by treatment with a solution of ammonium chloride in water.

10) A process in accordance with any one of the preceding process claims, wherein the partial hydrogenation of an ethynyl value of the group R (which has the significance given in claim 1) is carried out in the presence of a lead-inhibited palladium catalyst.

11) A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the examples given.

W. D. WHITAKER,
Patent Agent.
For Roche Products Limited.

PROVISIONAL SPECIFICATION

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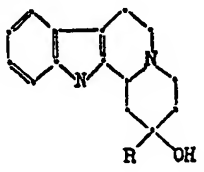
The present invention is concerned with novel quinolizine derivatives (more particularly, indolo[2,3-a]quinolizine derivatives) and with a process for the manufacture thereof.

The novel indolo[2,3-a]quinolizine derivatives provided by the invention are substances of the general formula:



in which R stands for an aryl, alkyl, alkenyl or alkynyl group; that is to say, they are 2 - R - 2 - hydroxy - 1,2,3,4,6,7,12,12b - octahydro - indolo[2,3 - a]quinolizines. They have a sedative and hypotensive activity and are intended for use in medicine.

According to the process provided by the invention, the novel substances aforesaid are manufactured by treating 2 - oxo - 1,2,3,4,6,7,12,12b - octahydro - indolo[2,3 - a]quinolizine with GRIGNARD reagent of the formula R—Mg—Halogen or a metallo-hydrocarbon of the formula R—metal (wherein in both formulae R has the same significance as given hitherto) under conditions which minimise the precipitation of the resulting metal complex, hydrolysing said complex and, if desired, hydrogenating the resulting 2 - R - 2-hydroxy - 1,2,3,4,6,7,12,12b - octahydro-indolo[2,3 - a]quinolizine (wherein R has the

same significance as given hitherto) so as to reduce any multiple bond contained in the group R therein.

The oxo compound used as the starting material is a known compound [GROVES and SWAN, J.C.S., 1952, 650].

Preferred metallo-hydrocarbons are lithium-aryls, -alkyls, -alkenyls and -alkynyls.

When carrying out the treatment with the GRIGNARD reagent or a metallo-hydrocarbon, it should be borne in mind that the metal compound also reacts at the indolic >NH of the oxo compound used as the starting material. Accordingly, it is necessary to use sufficient GRIGNARD reagent or metallo-hydrocarbon to cater for this. It is also necessary to carry out the treatment under conditions which prevent the precipitation of the metallo-indolyl complex. If the treatment is carried out in the most usual solvents for GRIGNARD and metal-alkyl reagents (e.g. diethyl ether) there is an immediate precipitate of insoluble complex and no reaction occurs with the ketone. It is therefore necessary to use solvent in which the said complex is soluble. Dry anisole has been found a useful solvent when using a GRIGNARD reagent and dry toluene has been found suitable when using alkyl-lithium compounds. The treatment using a lithium-acetylide can be carried out in anhydrous liquid ammonia.

A suitable method for hydrolysing the metal complex formed by the said treatment is to treat the complex with a solution of ammonium chloride in water. The hydrogenation of those hydrolysis products which contain alkenyl or alkynyl groups in position 2 may be effected using the usual hydrogenation catalysts. The alkynyl can be partially hydrogenated by hydrogenation in the presence of lead-inhibited palladium catalysts.

In order that the process of the invention may be more clearly understood and readily carried into effect, the following examples are now given:—

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